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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/021,660	02/10/98	BARON M	1877-110

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EXAMINER	
KAUFMAN,C	
ART UNIT	**PAPER NUMBER**
1646	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/021,660	Applicant(s) BARON ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *03 March 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *03 March 2000* is: a)☒ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The amendment filed 3/3/00 has been entered. It is noted that there was not request to amend the application by adding the abstracted submitted at the end of Applicant's reply. Until such a request is submitted the specification remains objected to for missing an abstract.

Response to Arguments

Previous rejections are moot in view of the cancellation of the claims except as they pertain to the new claims as set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 3/3/00 have been approved.

Specification

The amendment filed 3/3/00 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The deletion of the definition of "Synergistic effect" on page 11 of the specification presents new matter. The reasons for this is that the original definition in the specification is consistent with but more limiting than the meaning as the term is generally used in the art. Applicants are allowed to narrow the meaning of terms in the application, but once done, the meaning cannot then be expanded.

Applicant is required to add back what was deleted in the reply to this Office Action.

Claim Objections

Claims 60 and 61 are objected to because of the following informalities: "bone morphogenetic protein" is incorrect. The second word should be "morphogenic" (see *e.g.*, page 18, line 24 of specification). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 61, 62, 76-79, 81 and dependent claims 58-60, 63-75 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is indefinite because it is unclear what is encompassed by a WNT compound. There is not definition in the specification and the prior art has not set forth a limited definition of such a compound. The claim is also indefinite because it is unclear what the second compound *comprises* beside TGF-ß. That information is important because without it, it is unclear if the TGF-ß is the active ingredient of the second compound.

Claim 57 recites the limitation "one or more compounds " in line 6. There are only two compounds listed in the claim. There is insufficient antecedent basis for this limitation in the claim. There is, however, antecedent basis for a first and second compound, so that the claim could read instead "said first and optionally said second compound". It appears from the claim that the first compound must be present.

Claim 61 recites the limitation "the bone morphogenetic protein" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 57 does not recite that type of proteins, however, claim 60 does.

Claim 62 is indefinite because it is unclear where in the step of claim 57 the further step of the instant claim occurs.

Claim 76 is indefinite because it is unclear what the relationship between steps (a) and (b) are. It is unclear if the contacting leads to the stimulation or if it is an independent unrelated step.

Claim 77 is indefinite because it is unclear where in step (a), the selection is to occur. Additionally, the claim is indefinite because it is unclear how to select the compound, and if the compound is cDNA and/or the protein expressed from a cDNA.

Claim 78 is indefinite because the relationship between the selecting and screening is unclear. That is, it is unclear if one selects a compound and then screens the library of compounds.

Claim 79 is indefinite because extraembryonic tissue does not encode proteins. Also, It is unclear if the compound or library is capable of stimulating.

Claim 79 is indefinite because in step (a) it is confusing as it is written where biological activity consists of at least on of the listed activities. This rejection could be obviated by using a phrase such as, "for at least one biological activity selected from the group consisting of hematopioetic activity,...".

Claim 79 recites the limitation "the compound" in section (b). There is insufficient antecedent basis for this limitation in the claim. Section (a) refers only to compounds (plural). While the preamble may be used to breath life and meaning into a claim, it cannot be used for antecedent basis.

Claim 81 is indefinite because a functional assay cannot be a cell type. It is not clear what "cultured mammalian epiblast assays" are. If it is intended that the functional assay uses the listed types of cells, then this rejection could be obviated by using phrasing such as " wherein the functional assay utilizes a cell selected from..." in conjunction with deletion of the term " assays" at the end of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57, 60-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office Action beginning at line 25 on page 5, with the exception that it is agreed with Applicant's argument that there is description of vascular proliferation (*i.e.*, endothelial cell proliferation and differentiation) by visceral endoderm (*e.g.* page 39, first paragraph).

The new claim 76 is drawn to contacting cells with an extraembyronic tissue derived compound. Applicants point to page 34, lines 17-21 of the specification for support of such contact. The application at that section describes the requirement of contact with visceral endoderm or a compound therefrom, but does not provide support for the broader extraembyronic tissue derived compound.

Applicants argue that the specification describes how compounds from extraembryonic tissue may be used to stimulate at least one of hematopoiesis, endothelial cell proliferation and differentiation in undifferentiated mesodermal cells, so the invention has been adequately described. The argument has been fully considered, but is not persuasive. The claims are drawn to a method using a compound. There are a great multitude of compounds in extraembryonic tissue. Which specific compound(s) is the active one(s) is not stated in the claims. As stated in the previous rejection, 3 hedgehog compounds and BMP-4 have been shown to function in the claimed method. There is not description of other specific compounds. If the claim were drawn to a method of using, say extraembryonic tissue, then such a method would be described because the specification describes explant cultures in which an extraembryonic tissue mass is shown to stimulate hematopoiesis in undifferentiated mesoderm. The claims are not that broad, however, and require a compound (a narrow term compared to the term "tissue"). Therefore, the specification does not support description for the breadth of compounds.

Applicant argues that the specification presents examples demonstrating selective vascular growth. The argument has been fully considered, but is not persuasive. The specification shows only that visceral endoderm (p. 39) can lead to expression of endothelial cell markers such as Flk-1 and Vezf-1. It does not describe any specific compound that does that.

Therefore, the specification fails to provide an adequate written description for the broadly claimed method.

Applicant argues (second paragraph of page 14 of response) that as a method drawn to using a class of compounds to stimulate one of 3 specific biological effects, it is not necessary to describe all compounds that would work in the method. The argument has been fully considered, but is not persuasive. While it is true that claims drawn to methods do not necessary need the same narrowness as claims drawn to specific compounds of a class of compounds, under 35 USC 112, first paragraph, one must still be able to envision the class of compounds based on the written description of the specification. With the exception of hedgehog and BMP compounds, there is no description of compounds which induce hematopoiesis as required by the method and no specific compounds that stimulate endothelial proliferation or differentiation. It does not appear that Applicant was in possession of compounds other than those just mentioned that could be used in the claimed method.

Applicants argue that Amgen v. Chugai sets forth that conception occurs when one "is able to define [a chemical] by its method of preparation". This is not persuasive. In *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ2d, 1016 (CAFC 1991), the compound at issue is a gene, but the same finding holds for proteins. The court stated that:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See *Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when and inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

Therefore, according to the court, one must be able to distinguish the compound from others. There is nothing to distinguish the extraembryonic tissue derived compound in the instant claims **except** its biological property and the tissue origin it shares with a multitude of other compounds

which may or may not have the necessary biological property. This type of description the court held as insufficient. Additionally, to prepare a compound, one would have to know not only what tissue it is derived from, but how to isolate it (*e.g.*, purification parameters are required for specific isolation). As a result, a method of the compound's preparation is not described in the instant specification.

Claims 57 and 60-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the reasons set forth in the previous Office Action beginning at line 7 on page 7, and for the following reasons addressing the new claims. There is no showing of a WNT compound in the instant application or prior art that is both derived from extraembryonic tissue and able to stimulation at least one of hematopoiesis, endothelial cell proliferation and differentiation in undifferentiated mesodermal cells. Additionally, it has been shown in the prior art that there are many WNTs and they do not all have the same activity, so which WNT would function in this method is not disclosed or known. Therefore, the claimed method using WNT is not enabled.

Applicants argue that only routine experimentation is necessary to practice the full scope of the instant invention, unlike the experimentation that would have been required relating to *In re Wands*. The argument has been fully considered, but is not persuasive. In the instant situation, Applicant has provided an invitation to experiment without a reasonable expectation of success. It is not disclosed in the specification or prior art what compounds besides Ihh, Shh, Dhh and BMP-4 and-2 would be reasonably expected to be derived from extraembryonic tissue and stimulate at least one of hematopoiesis, endothelial proliferation and differentiation. As stated at the beginning of page 10 of the previous Office action, the compound is being described by what it does, not be what it is. By requiring a "compound", the claims have a narrower breadth than if "visceral endoderm" was required. Because of the vast number of compounds within extraembryonic tissue and the unknown physical characteristics and biological activities of those compounds as related to the current invention, it would require not routine but undue experimentation to practice the invention commensurate in scope with the claims.

Applicant argues that predictability concerning whether a compound might induce hematopoiesis is not low because data demonstrating activity has been provided and methods to test for such activity are also provided. The argument has been fully considered, but is not persuasive. Indeed the predictability of specific compounds is low, with the exception of those few shown in the specification to have the required property. As described in the preceding paragraph, "visceral endoderm" has been shown to induce hematopoiesis, but which of the mass of compounds derivable from visceral endoderm has that property is not disclosed. Providing methods of testing for the activity are an invitation to experiment without a reasonable expectation of success. Protein purification is not trivial, and identifying individual compounds from a tissue which have a specific function would require undue experimentation in part because which of individual compounds would be reasonable expected to have the required property is unpredictable outside the family of compounds which are hedgehog or bone morphogenic proteins.

Claim Rejections - 35 USC § 102

In response to Applicant's argument that more than one reference should not be used in making a rejection under 35 USC 102, it is noted that only a single reference was relied upon for each independent rejection under 35 USC 102. Therefore, Applicant's argument does not apply.

Claims 57,62-64, 69 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Zeigler et al. (V, Blood, 1994) for the reasons set forth in the previous Office Action at the top page 12.

Applicant argues that the reference teaches away from the present invention of stimulation of at least one of hematopoiesis, endothelial proliferation and differentiation because the compound, TPO, effects megakaryocytes and thrombopoiesis. The argument has been fully considered, but is not persuasive. Thrombopoiesis is the process of platelet production which is part of hematopoiesis. Hematopoiesis is a broad term describing many processes such as thrombopoiesis, red blood cell production and white blood cell production. Therefore, stimulation of thrombopoiesis is stimulation of hematopoiesis.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. Kaufman

Patent Examiner, Art Unit 1646

June 2, 2000

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER